Public Assessment Report

Scientific discussion

Name of the Product
Olmesartan medoxomil Teva
10 mg, 20 mg and 40 mg film-coated tablets

(olmesartan medoxomil)

Procedure number:
HU/H/0227/001-003/DC

Marketing authorisation holder: Teva Magyarország Zrt. Hungary

Date: 19 February 2013

CONTENT

LAY SUMMARY

The National Institute of Pharmacy Directorate of the National Institute for Quality- and Organizational Development in Healthcare and Medicine, after careful assessment of the quality and therapeutic benefit/risk (non-clinical and clinical) aspects on the basis of the submitted documentation, authorised the Olmesartan medoxomil Teva 10 mg, 20 mg and 40 mg film-coated tablets for marketing.

The main characteristics of the medicinal products are summarised below.

The *active substance* is olmesartan medoxomil. Each film-coated tablets contain 10 mg, 20 mg or 40 mg of this active principle. The *other ingredients* are:

tablet core:

- lactose monohydrate
- microcrystalline cellulose
- low-substituted hydroxypropyl cellulose
- magnesium stearate.

film coating: Opadry II 85F18378 white [poly(vinyl alcohol) - partly hydrolyzed, titanium dioxide (E171), macrogol 3350 (polyethylene glycol), talc].

How Olmesartan Medoxomil Teva film-coated tablets look like

10 mg film-coated tablets: white, round standard convex, film-coated tablets, debossed with “O” on one side and “10” on the other side;
20 mg film-coated tablets: white, round standard convex, film-coated tablets, debossed with “O” on one side and “20” on the other side;
40 mg film-coated tablets: white, oval shaped, film-coated tablets, debossed with “O” on one side and “40” on the other side.

The film-coated tablets are packaged in blister packs.

What Olmesartan medoxomil Teva film-coated tablets are and what they are used for

Olmesartan medoxomil Teva film-coated tablets contain the active substance olmesartan medoxomil, which belongs to a group of medicines known as angiotensin II antagonists. The angiotensin II antagonist works by causing blood vessels to relax, which in turn lowers blood pressure.

Olmesartan medoxomil Teva tablets are used for the treatment of patients who suffer from high blood pressure with no specific cause.

Before you take Olmesartan medoxomil Teva

Do not take this medicinal product

- if you are allergic (hypersensitive) to olmesartan medoxomil or any of the other ingredients of these tablets

- if you are more than 3 months pregnant. (It is also better to avoid Olmesartan medoxomil Teva in early pregnancy – see Pregnancy section.)
- if your bile ducts are blocked due to gallstones, tumour or inflammation resulting in jaundice (yellowing of the skin).

Before treatment with Olmesartan medoxomil Teva tell your doctor if any of the following apply to you:
- if you have had severe vomiting, diarrhoea or depletion of water and salt in your body,
- if you suffer from kidney or liver problems, and/or if you have had kidney transplant,
- if you have a heart condition including problems with your heart muscle and valves
- if you have increased levels of potassium in your blood,
- if you have problems with your adrenal gland,
- if you are under the age of 18 years as olmesartan medoxomil has not been studied in this population group,
- if you think you are (or might become) pregnant. Olmesartan medoxomil Teva is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at this stage (see Pregnancy section).

Please tell your doctor or pharmacist i*f you are taking or have recently taken any of the following medicines* as they may interact with Olmesartan Medoxomil Teva:
- lithium (used to treat mood swings and certain types of depression). Lithium toxicity may increase if used at the same time as olmesartan medoxomil. Your doctor may therefore need to measure your lithium blood levels;
- potassium supplements,water tablets (diuretics) or heparin (used to thin blood) may increase the potassium level in the blood;
- other blood pressure lowering medicines as the effect of olmesartan medoxomil may increase;
- non-steroidal anti-inflammatory drugs (NSAIDs) which are used to reduce pain, fever and inflammation may increase the risk of kidney failure and also decrease the effect of olmesartan medoxomil;
- certain indigestion remedies (antacids) containing aluminium magnesium hydroxide as the effect of olmesartan medoxomil can be slightly reduced.

Olmesartan medoxomil Teva can be taken *with or without food*. Your recommended daily dose of tablets should be swallowed with a little water, preferably at the same time each day. Do not chew the tablet.

Pregnancy and breast-feeding

Pregnancy: you must tell your doctor if you are (or might become) pregnant. Your doctor will normally advise you to stop taking Olmesartan Medoxomil Teva before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Olmesartan Medoxomil Teva. Olmesartan Medoxomil Teva is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby.

Breast-feeding: tell your doctor if you are breast-feeding or about to start breast-feeding. Olmesartan Medoxomil Teva is not recommended for mothers who are breast-feeding, and

your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines: it is unlikely that Olmesartan medoxomil Teva will affect your ability to drive or operate machinery. However, dizziness or tiredness can occasionally occur during the treatment of high blood pressure. If you experience such effects, ask your doctor for advice before driving or using machinery.

Important information about some of the ingredients of Olmesartan Medoxomil Teva
Olmesartan Medoxomil Teva contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

How to take Olmesartan medoxomil Teva

Take it always as instructed by your doctor.

Olmesartan medoxomil Teva should be taken with a little water once a day at about the same time each day, with or without food, for example at breakfast.

The initial recommended dose is 10 mg once daily.

If your blood pressure is not adequately controlled at this dose, your doctor may increase it to an optimal 20 mg once daily dose.

If additional blood pressure reduction is required, then your doctor may increase your Olmesartan Medoxomil Teva dose to a maximum of 40 mg daily dose or hydrochlorothiazide therapy may be added.

Elderly: no adjustment of dosage is generally required in elderly patients. However, if you require a gradual increase of the dose up to the maximum dose of 40 mg daily, your doctor will monitor your blood pressure closely.

Patients with kidney problems: a dose of 20 mg daily is recommended for patients who have mild to moderate kidney problems. If you suffer from severe kidney problems, you should not take Olmesartan medoxomil Teva.

Patients with liver problems:

- no dose adjustment is required if you suffer from a mild liver problem;
- if you suffer from a moderate liver problems, a starting dose of 10 mg daily is recommended and should not exceed 20 mg daily. Your doctor will need to monitor your blood pressure and kidneys if you are already taking medicines to control their functions.;
- Do not use Olmesartan medoxomil if you suffer from severe liver problem.

Children and adolescents (less than 18 years): Olmesartan medoxomil Teva is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Black patients: as with other similar medicinal products the blood pressure lowering effect of olmesartan medoxomil is somewhat less in black patients.

If you take more Olmesartan Medoxomil Teva than you should, contact your doctor or go to your nearest hospital immediately where you will be carefully monitored. Please take your medicine pack with you. The most likely effect of overdose is low blood pressure (hypotension).

If you forget to take Olmesartan Medoxomil Teva: if you miss a dose, take it as soon as possible. However if it is nearly time for your next dose, skip the missed dose and carry on as before. Do not take a double dose to make up for a forgotten dose.

It is important to keep taking of Olmesartan medoxomil Teva unless your doctor tells you to stop.

Possible side effects

Like all medicines, Olmesartan medoxomil Teva can cause side effects, although not everybody experiences them. All medicines can cause allergic reactions, although serious allergic reactions are very rare.

You must stop taking Olmesartan medoxomil Teva and contact your doctor if you experience swelling of the face, mouth and/or larynx (voice box) together with itching and rash.

Rarely Olmesartan medoxomil Teva can cause the blood pressure to drop drastically resulting in severe light headedness or fainting. Should this occur, stop taking Olmesartan medoxomil Teva, contact your doctor and lie down flat.

The following adverse reactions have been reported during clinical trials of olmesartan medoxomil:

Common (that affects 1 to 10 users in 100):
- dizziness;
- bronchitis, sore throat, cough, muscle pain, flu-like symptoms, runny or stuffy nose;
- disorders of the digestive system such as stomach ache, diarrhoea, vomiting, indigestion (bloating and belching), inflammation of the stomach and feeling sick;
- inflammation of a joint or joints (arthritis), back pain, pain in the skeletal system;
- detection of blood in the urine, infection of the urinary tract;
- swelling of ankles, feet, legs, hands or arms;
- tiredness;
- chest pain;
- changes in different laboratory parameters, including increase in liver enzymes, kidney parameters such as creatinine, blood urea, blood lipids.

Uncommon (that affects 1 to 10 users in 1,000):
- spinning sensation (vertigo);
- pain or uncomfortable feeling in the chest (angina pectoris);
- rash;

- in the elderly, likelihood of decrease in blood pressure.

Rare (that affects 1 to 10 users in 10,000):
- decrease in blood pressure;
- increased potassium levels in the blood.

The following adverse reactions have been reported during post-marketing experience of olmesartan medoxomil:

Very rare (that affects less than 1 user in 10,000):
- reduced platelet count in the blood;
- increased potassium levels in the blood;
- dizziness, headache;
- cough;
- stomach pain, feeling sick, vomiting;
- itching of the skin, a widespread and symmetrically distributed eruption on the skin, allergy reactions of the skin, facial swelling;
- muscle cramp, muscle pain, weakness, lack of energy, general discomfort and uneasiness;
- damage to the kidneys and loss of kidney function;
- loss of energy, tiredness, feeling lazy, discomfort and uneasiness;
- increase in blood creatine and blood urea, increase in liver enzymes.

How to store Olmesartan medoxomil Teva

This medicinal product does not require any special storage conditions, but keep out of the reach and sight of children.

Scientific discussion during the initial procedure

This module reflects the scientific discussion for the approval of Olmesartan medoxomil Teva 10 mg, 20 mg and 40 mg film-coated tablets. The procedure was finalised (day 210) at 15 April 2010. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other* R*egulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member States concerned.

The applicant then the holder of the marketing authorisation was Teva Magyarország Zrt. Hungary.

This Decentralised Procedure application (reference member state, RMS: Hungary, concerned member states, CMS: Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Greece, Ireland, Latvia, Lithuania, Poland, Portugal, Romania, Slovenia, Slovakia and Spain) concerned the generic versions of olmesartan medoxomil film-coated tablets.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application) and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The originator product was Olmetec tablets from Daichii-Sankyo Europe, authorised for marketing since 2002 in the European Union.

The three strengths of tablets had the same qualitative compositions and are dose-proportional. They were manufactured according to the same manufacturing processes.

Based on the review of the quality, safety and efficacy data, the Member States have granted the marketing authorisation for olmesartan medoxomil 10 mg, 20 mg and 40 mg film-coated tablets.

The therapeutic indication is: treatment of patients who suffer from high blood pressure with no specific cause.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

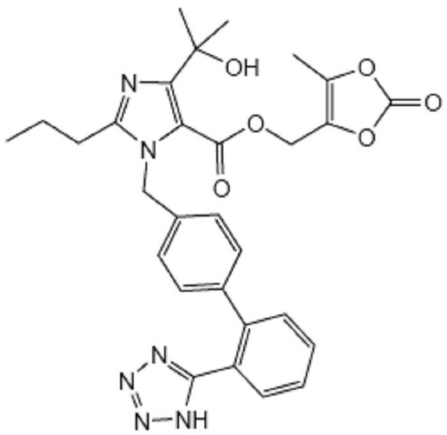
II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Olmesartan medoxomil Teva 10 mg, 20 mg, 40 mg film-coated tablets via a decentralised procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by TEVA Pharmaceutical Industries Ltd. The originator products were Olmetec tablets from Daichii-Sankyo Europe, authorised for marketing since 2002 in the European Union.

II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorisation dossier. The Quality Overall Summary is adequate.

INN name: olmesartan medoxomil
Chemical name: 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazole-5-yl) biphenyl-4-yl-methyl]imidazole-5-carboxylic acid 5-methyl-2-oxo-1,3-dioxol-4-ylmethyl ester
Structure:



The active substance is white to off white crystalline powder, slightly soluble in water, freely soluble in acetonitrile and absolute ethanol, practically insoluble in hexane.

It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by elemental analysis, NMR, MS, FT-IR, XRDP and by UV spectroscopy. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

During the assessment phase the substance was not official in the European Pharmacopoeia (Ph. Eur.), however, the current Ph. Eur. already includes a specific monograph for this API. The specification meets the requirements of this monograph; additional specification has only been set for residual solvents, particle size distribution.

The Ph. Eur. specification includes the following tests for olmesartan medoxomil: appearance, identification, assay, purity, water, heavy metals.

The presented specification is in accordance also with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Ph. Eur. are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on *genotoxic impurities*.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the re-test period proposed is acceptable with no special storage condition.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim of the pharmaceutical development was to develop film-coated tablets containing olmesartan medoxomil API in 10, 20, 40 mg doses pharmaceutically equivalent and bioequivalent to the reference medicinal products.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the film-coated tablets were shown to be similar to the reference product.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies products with the following appearance, composition and packaging were obtained:
- 10 mg film-coated tablets are white, round, convex, film-coated tablets, debossed with “O” on one side and “10” on the other side.
- 20 mg film-coated tablets are white, round, convex, film-coated tablets, debossed with “O” on one side and “20” on the other side.
- 40 mg film-coated tablets are white, oval, convex, film-coated tablets, debossed with “O” on one side and “40” on the other side.

The excipients used in the finished product were magnesium stearate, low-substituted hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose and Opadry white (talc, macrogol, titanium dioxide and poly(vinyl alcohol) – partly hydrolysed). All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is opaque Al//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with no special storage conditions is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical point of view there are no concerns regarding the marketing authorisation of Olmesartan medoxomil Teva 10 mg, 20 mg and 40 mg tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of olmesartan medoxomil are well known. As olmesartan medoxomil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Ecotoxicity/environmental risk assessment

Since Olmesartan medoxomil Teva 10 mg, 20 mg, and 40 mg film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment has been therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for this generic application from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract. Olmesartan blocks all actions of angiotensin II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin II. In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after cessation of therapy.

No new clinical studies apart from the bioequivalence study were submitted with this application. This is acceptable as one the one hand it was a generic application, on the other hand olmesartan medoxomil is a well known active ingredient and no clinical issues are considered to arise as a result of it inclusion in the proposed product.

The clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

IV.2 Pharmacokinetics

To support this application, the applicant has submitted one bioequivalence study. This study compared Olmesartan Medoxomil 40 mg Tablets (Teva Pharmaceutical Industries Ltd.) with Olmetec® 40 mg Tablets (Sankyo Pharma UK Limited, UK).

The study was a randomized, open label, two-treatment, two period, single dose crossover bioequivalence study in healthy human adult subjects, under fasting conditions.

Following a washout period, the subjects received the alternative formulation under identical conditions. During each study period, blood samples were taken pre-dose and at defined time-points after the administration. Plasma was harvested from these samples and assayed for olmesartan using a validated LC/MS/MS method.

The *biowaiver* in respect of the other strengths is justified, and is in line with criteria of the CHMP *Note for Guidance on Investigation of Bioavailability and Bioequivalence*.

Results of this bioequivalence study are shown in the Table below.

Pharmacokinetic parameters
(non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	8343.99	8558.54	1368.82	1.91
Reference	8540.84	8706.99	1372.43	1.94
***Ratio (90% CI) T vs. R**	98.29	97.86	98.79	–
90% CI	91.58-105.50	91.21-104.99	91.76-106.36	–

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

*ln-transformed values

In conclusion it can be seen that the confidence intervals and point estimators of both AUC_{0-t} and C_{max} were fully in the 0.8-1.25 confidence interval. Therefore, Olmesartan Medoxomil-TEVA 40 mg film-coated exhibited equivalent rate and extent of absorption to Olmetec 40 mg Tablets in healthy subjects after an oral single-dose, under fasting conditions. ANOVA did not detect a significant difference between Test and Reference products for any of the pharmacokinetic parameters of interest. These data demonstrate that there were no important pharmacokinetic differences between the Test and Reference products in this study.

IV.3 Pharmacodinamics

No new clinical data were submitted since the application referred to the bioequivalence with the reference product.

IV.4 Clinical efficacy

No new clinical studies apart from the above bioequivalence study were submitted with this application. This is acceptable as olmesartan medoxomil is a well known active ingredient and no clinical issues are considered to arise as a result of it inclusion in the proposed product.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted with this application and none were required.

No new or unexpected safety concerns were raised during the bioequivalence study.

IV.6 Discussion on the clinical aspects

The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application concerns a generic version of olmesartan medoxomil. The requested indication was treatment of patients who suffer from high blood pressure with no specific cause. The active substance has been widely and safely used, the application of the present products does not pose any new risk.

The submitted documentation is formally adequate and scientifically sound. The benefit/risk assessment is positive. There is nothing against granting the marketing authorisation.

V.1 Conditions for the marketing authorisation

V.1.1 Requirements for specific post-marketing obligations

Not needed.

V.1.2 Pharmacovigilance system

The RMS considers that the Pharmacovigilance system submitted by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

V.1.3 Risk Management Plan

No description of the Risk Management System had to be provided since the application concerned a medicinal product containing a known active substance for which no safety concern requiring additional risk minimisation activities has been identified.

V.1.4 Periodic Safety Update Report (PSUR)

The Company requested a PSUR cycle waiver for this product to go immediately into a three year cycle. The originator product is Olmetec tablets from Daichii-Sankyo Europe. The PSUR Work Sharing List – status June 2009 (http://www.hma.eu/uploads/media/PSUR_Work_Sharing_List_June_2009.pdf), the EU Harmonised Birth Day of olmesartan and the next Data Lock Point should be taken into account.

V.1.5 Legal status

Prescription-only medicine.

V.2. Summary of Product Characteristics (SmPC)

The SmPC has been adequately harmonized with that of the originator product and is acceptable.

V.3 Package leaflet and user consultation

The package leaflet (PIL) has been evaluated via a user consultation in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the *readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
II.: new alternative intermediate manufacturer	HU/H/0227/001-003/II/001	No	15. 06. 2011	03. 02. 2012	Approval	No
IA.: Name change of MAH in ES, change of address of MAH in PT, name of finished product manufacturer in ES	HU/H/0227/1A/002/G	Yes	12.07.2011	11.08.2011	Approval	No
IB.: Product name change in DK, PT, SK	HU/H/0227/001-003/IB/003	Yes	07.07.2011	06.08.2011	Approval	No
IA: deletion of a batch release and control site and addition of a new one	HU/H/0227/IA/004/G	No	12. 04. 2012	12. 05. 2012	Approval	No